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SYNTHESIS OF THE STEREOISOMERS OF THE METHYLESTERS OF 3-ISOPROPYL-5-METHOXY-6-KETOHEPTANOIC ACID AND OF 2-METHOXY-4-ISOPROPYLHEXANDIOIC ACID

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Abstract—The four stereoisomers of 3-isopropyl-5-methoxy-6-ketoheptanoic acid methylester and those of 2-methoxy-4-isopropylhexandioic acid methylester were synthesized from *R*(−)- and *S*(+)-carvone. The combined data given provide a basis for specific enantiomer assignment to natural product degradation materials.

In order to determine the absolute configuration of centres C-7 and C-9 of agerol[1] and of ageratriol,[2] sesquiterpene alcohols isolated from *Achillea ageratum*, it was necessary to prepare the four stereoisomers (**10a, b, c, d**) of the methylester of 3-isopropyl-5-methoxy-6-ketoheptanoic acid and those (**11a, b, c, d**) of the methylester of 2-methoxy-4-isopropylhexandioic acid, which could be useful also for the determination of configurations of similar natural products.

They were obtained starting from the carvotanacetols **4**, the absolute configurations of which are known,[3] in accordance with the reported Scheme.

The *cis*-carveols **5** were obtained at 99% purity from *R*(−)- and *S*(+)-carvone by slightly modifying the method of Reitsema.[4] The subsequent catalytic reduction of the exocyclic double bond is very selective working with the hindered pivaloyl ester **6**, instead of the free alcohol **5**; after saponification, the *cis*-carvotanacetols were obtained in a very pure (99%) state.

In order to obtain the *trans*-carvotanacetols we adopted the procedure reported in the Scheme instead of that described,[6] since the yields are higher and the products purer.

The methylethers **8a, b, c, d**, are obtained from the carvotanacetols either with CH_2N_2–BF_3·Et_2O or with NaH–CH_3I.

3 - isopropyl - 5 - methoxy - 6 - ketoheptaldehydes **9a, b, c, d**, obtained by ozonolysis of the carvotanacetol methylethers, degenerated quickly and were sensitive to temperature change. They were obtained with a maximum of 90–92% purity by silica-gel chromatography. The diastereoisomers are indistinguishable in GLC. The NMR (60 MHz) spectra ($CDCl_3$) reveal significant differences (Table); the hydrogen signals of the two geminal methyls appear as a doublet in the enantiomers **9c** and **9d**, while they appear as a pair of doublets in the enantiomers **9a** and **9b**.

The ketoesters **10a, b, c, d**, obtained by permanganate oxidation, are also indistinguishable under normal GLC conditions; only on SCOT column (DEGS, 50 feet) does slight separation occur, the enantiomers **10a** and **10b** being those with the lowest retention times. The two pairs of enantiomers are easily distinguishable by NMR; the geminal methyls being magnetically equivalent in the **10c** and **10d** enantiomers and not equivalent in the **10a** and **10b** enantiomers. The stability of these derivatives is rather limited; in particular, compounds **10c** and **10d** epimerize in C-5 on standing.

The cleavage of ketoesters **10** to hexandioic acid methylesters **11** was effected by sodium hypoiodite;† a small inversion in C-2 (*ca* 8%) occurs only in the case of enantiomers **11a** and **11b**. As for compounds **10**, the diastereoisomers are only partially separated on SCOT column (DEGS, 50 feet). Again the methyls NMR pattern (Table) is identical to that of the derivatives previously described.

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†Enolisation, which could destroy C-5 asymmetry, is the rate-limiting step in base-catalysed iodination, which is practically irreversible.[7]

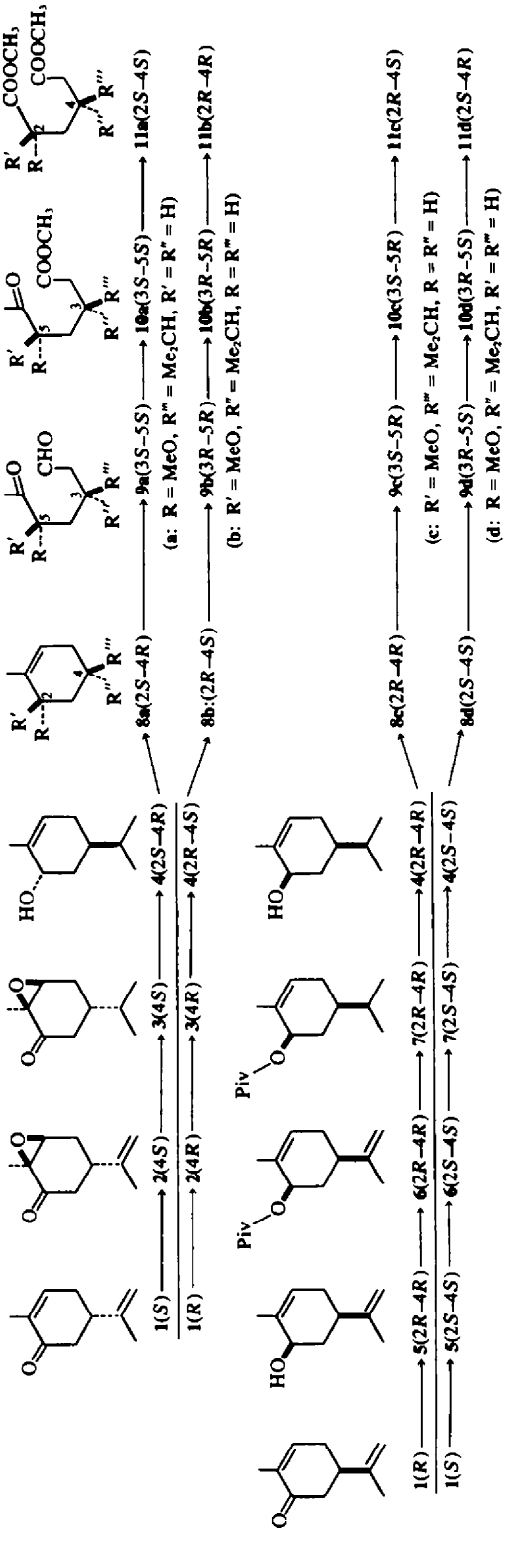

Table 1.

	$[\alpha]_D^{22}$	Me_2CH	NMR ($CDCl_3$, δ values) MeO	MeCO	CHO	COOMe
9a	−60·12(*c* 2·1 CCl_4)	0·85 d(J 6 Hz);	3·23 s	2·12 s	9·91 t	
9b	+60·43(*c* 2·3 CCl_4)	0·89 d(J 6 Hz).				
9c	+52·50(*c* 2·1 CCl_4)	0·86 d(J 6 Hz)	3·28 s	2·16 s	10·1 t	
9d	−51·16(*c* 1·9 CCl_4)					
10a	−56·10(*c* 2·0 MeOH)	0·86 d(J 6 Hz);	3·31 s	2·08 s		3·69 s
10b	+55·36(*c* 2·1 MeOH)	0·90 d(J 6 Hz).				
10c	+32·61(*c* 2·2 MeOH)	0·87 d(J 6 Hz)	3·32 s	2·16 s		3·65 s
10d	−34·11(*c* 2·1 MeOH)					
11a	−33·03(*c* 2·4 MeOH)	0·88 d(J 6 Hz);	3·36 s			3·70 s;
11b	+34·60(*c* 3·0 MeOH)	0·91 d(J 6 Hz).				3·80 s.
11c	+50·17(*c* 1·9 MeOH)	0·87 d(J 6 Hz)	3·37 s			3·67 s;
11d	−52·24(*c* 2·1 MeOH)					3·76 s.

If the data summarized in the Table are taken into account it will be seen that it is fairly easy to assign the absolute configuration to these acyclic derivatives simply on the basis of the rotatory power and the NMR spectrum. In the case of all isomers with *S–S* or *R–R* configuration, recognisable on account of the double doublet of the geminal methyls in the NMR spectrum, the (−) sign of the rotatory power characterises the compounds with the isopropyl group of *S* configuration; in the case of enantiomers *S–R* or *R–S*, recognisable by the NMR single doublet of the geminal methyles, the (−) sign characterises the compounds with the isopropyl group of *R* configuration.

EXPERIMENTAL

M.ps were determined with a Mel-Temp apparatus and are uncorrected. IR spectra were determined with a Perkin Elmer 257 instrument. NMR spectra were recorded on a Jeol instrument at 60 MHz, with TMS as internal standard, chemical shifts have been recorded in δ values. Optical rotations were measured on a Perkin Elmer 141 instrument. The purity of products were all checked by GLC and TLC.

cis-*Carveols*[4] [5(2R–4R) *and* 5(2S–4S)]. To a stirred suspension of LAH (28 g) in dry Et_2O (50 ml), cooled at −10°, a soln of purified *R* (or *S*)-**1** (25 g) in dry Et_2O (50 ml) was added dropwise over 2 h. Then LAH powder (0·6 g) was added in small portions until carvone was consumed (GLC) (4–5 h). 15% HCl (100 ml) was added with caution (−5/−10°) and the temp of the stirred mixture was allowed to rise to 20°. The organic layer, washed with 5% $NaHCO_3$ aq, then with H_2O and dried ($MgSO_4$). After evaporation the residue taken up in pentane (50 ml). The product crystallized from pentane soln at −32°; when the ratio *cis*-/*trans*-carveol in the supernatant liquid was *ca* 3:1 (GLC, carbowax 20M 20% on chromosorb W, t. 170°), the soln was decanted and the crystalline product washed with a little pentane. The compound was purified (99%) by distillation (18 g), b.p. 101°/10 mm, m.p. 25·5–26·5°. IR (film): 3320 cm^{-1}; NMR ($CDCl_3$): 1·7 (6H, s, CH_3—C=); 4·1 (1H, m, H—C—O); 4·64 (2H, s, CH_2=C); 5·37 (1H, br.s, H—C=C).

5(2*R*–4*R*): α_D^{22} −21·8° $[\alpha]_D^{22}$ −30·0° (*c* 2·1 MeOH) (lit[6b] α_D^{24} −20·47°).

5(2*S*–4*S*): α_D^{22} +21·9° $[\alpha]_D^{22}$ +30·4° (*c* 2·0 MeOH) (lit[6a] α_D^{25} +22·8°; $[\alpha]_D^{25}$ +23·9°).

cis-*Carvotanacetols* [4(2R–4R) *and* 4(2S–4S)]. To a stirred soln of (+)- or (−)-*cis*- **5** (15·2 g) and dry pyridine (11·8 g) in Et_2O (60 ml), pivaloyl chloride (12·6 g) was added at 0°. After 36 h at room temp, usual work up afforded the ester **6**, which was purified (99%) by distillation, (21·5 g), b.p. 137–8°/17 mm. (Found: 6(2*R*–4*R*) C, 76·41; H, 10·03; 6(2*S*–4*S*) C, 76·08; H, 10·09. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·23%).

A suspension of **6** (20 g) and Ni–Raney (0·7 g) in MeOH (250 ml) was reduced with H_2 at room temp and pressure (12 h). The catalyst was filtered off, 5N KOH (20 ml) added and the soln heated on a water bath for 5 h. The solvent was removed *in vacuo* and the product extracted with Et_2O. After evaporation, the residue was purified (99%) by distillation (11·5 g), b.p. 122–3°/15 mm; IR (film): 3310 cm^{-1}; NMR ($CDCl_3$): 0·87 (6H, d(J 6 Hz), CH_3—C); 1·72 (3H, s, CH_3—C=); 4·07 (1H, m, H—C—O); 5·38 (1H, m, H—C=C).

4(2*R*–4*R*): α_D^{22} − 19·54° $[\alpha]_D^{22}$ − 28·21° (*c* 2·5 MeOH) (lit[5] α_D^{23} − 20·70).

4(2*S*–4*S*): α_D^{22} + 19·85° $[\alpha]_D^{22}$ + 28·38° (*c* 2·3 MeOH).

Epoxy-carvones [2(4S) *and* 2(4R)]. The epoxycarvones, obtained according to Klein and Ohloff[9] (94–95% of purity), were purified by dissolving the compound (25 g) in n-pentane (100 ml), then cooling the soln at −35° for 48 h. The solvent was decanted and the crystalline residue purified (99%) by distillation (21 g), b.p. 100°/6 mm; IR (film): 1705 cm^{-1}; NMR ($CDCl_3$): 1·37 (3H, s, CH_3—C—O); 1·68 (3H, s, CH_3—C=); 3·42 (1H, m, H—C<O>C); 4·67 (2H, m, CH_2=C). 2(4*S*): α_D^{22} − 92·60° $[\alpha]_D^{22}$ − 81·20° (*c* 2 MeOH) (lit[9] $[\alpha]_D^{20}$ − 88·00° ($CHCl_3$)), 2(4*R*): α_D^{22} + 92·85° $[\alpha]_D^{22}$ + 81·02° (*c* 2 MeOH) (lit[9] $[\alpha]_D^{20}$ + 87·60° ($CHCl_3$)).

Epoxy-dihydrocarvones [3(4S) *and* 3(4R)]. A soln of **2** (20 g), tris - (triphenylphosphine) - chlororhodium (1 g) in benzene (150 ml), was reduced with H_2 at room temp and pressure (10 h). n-Pentane (200 ml) was added and the mixture filtrated over silica gel. The solvents were distilled off and the residue isolated and purified (99%) by distillation *in vacuo* (18·5 g), b.p. 93°/3 mm; IR (film): 1705 cm^{-1}; NMR ($CDCl_3$): 0·89 (6H, d (J 6 Hz), CH_3–C); 1·37 (3H, s, CH_3—C—O); 3·36 (1H, d (J 3 Hz), H—C<O>C). (Found: *3(4S)* C, 71·19; H, 9·40; *3(4R)* C, 71·46; H, 9·44. $C_{10}H_{16}O_2$ requires: C, 71·39; H, 9·58%). *3(4S)*: α_D^{22} − 100·65° $[\alpha]_D^{22}$ − 102·13° (*c* 2 MeOH). *3(4R)*: α_D^{22} + 100·35° $[\alpha]_D^{22}$ + 102·02° (*c* 2 MeOH).

trans-*Carvotanacetols* [4(2S–4R) *and* 4(2R–4S)].[9] To a stirred soln of (+) or (−) **3** (18 g) in MeOH (120 ml) 98%

hydrazine hydrate (12·8 g) was added dropwise at 0°. After 30', 7% methanolic AcOH (15 ml) was added with cooling so as not to allow the temp to exceed 2–3°. The mixture was kept at this temp for 6 h and then worked up by pouring into ice-water (150 ml) and extracting with CH_2Cl_2. The solvent was distilled off affording a yellow oil which was purified (98%) by two distillations *in vacuo* (9·8 g), b.p. 115°/22 mm; IR (film): 3300 cm^{-1}; NMR ($CDCl_3$): 0·88 (6H, d(J 6 Hz), CH_3—C); 1·77 (3H, s, CH_3—C=); 3·96 (1H, t(J 3 Hz), H—C—O); 5·56 (1H, m, H—C=C). *4(2S–4R)*: $\alpha_D^{22} - 161·82°$ $[\alpha]_D^{22} - 152·0°$ (*c* 2 MeOH) (lit[5] $[\alpha]_D^{23} - 187·3°$). *4(2R–4S)*: $\alpha_D^{22} + 161·21°$ $[\alpha]_D^{22} + 151·4°$ (*c* 2 MeOH) (lit[5] $\alpha_D^{20} + 169·12°$).

Carvotanacetol methylethers (**8a, b, c, d**). NaH (80% oily dispersion, 5·2 g) was added, during 30 min, to a stirred soln of **4** (15·4 g) in dry THF (120 ml). MeI (20 g) was then added dropwise and the stirring continued for 5 h at 40°. MeOH (5 ml) was added and the mixture poured into water (200 ml). Extraction with Et_2O and evaporation of the solvent afforded an oil, which was purified by distillation (14·1 g), b.p. 90–93°/14 mm. **8a**: $\alpha_D^{22} - 82·80°$ $[\alpha]_D^{22} - 97·50°$ (*c* 2 MeOH). **8b**: $\alpha_D^{22} + 83·22°$ $[\alpha]_D^{22} + 97·84°$ (*c* 2 MeOH). NMR ($CDCl_3$): 0·88 (3H, d(J 5 Hz), CH_3—C); 0·91 (3H, d(J 5 Hz), CH_3—C); 1·75 (3H, s, CH_3—C=); 3·37 (3H, s, CH_3—O); 3·43 (1H, m, H—C—O); 5·55 (1H, m, H—C=C). **8c**: $\alpha_D^{22} - 88·42°$ $[\alpha]_D^{22} - 98·31°$ (*c* 2 MeOH). **8d**: $\alpha_D^{22} + 88·27°$ $[\alpha]_D^{22} + 98·04°$ (*c* 2 MeOH). (NMR ($CDCl_3$): 0·86 (6H, d(J 6 Hz), CH_3—C); 1·6 (3H, s, CH_3—C=); 3·21 (3H, s, CH_3—O); 3·55 (1H, m, H—C—O); 5·30 (1H, m, H—C=C). (Found: **8a** C, 78·40; H, 12·04; **8b** C, 78·56; H, 11·81; **8c** C, 78·64; H, 11·89; **8d** C, 78·70; H, 12·15. $C_{11}H_{20}O$ requires: C, 78·51; H, 11·98%).

3 - *Isopropyl* - 5 - *methoxy* - 6 - *ketoheptanals* (**9a, b, c, d**). The methylether **8** (8·35 g) in AcOH (40 ml) was chilled to 5–8° and a stream of ozonised (5%) O_2 passed into it. Zn powder (8 g) was then added and the mixture allowed to stand under N_2 for 24 h at room temp, then filtered. The filtrate was evaporated *in vacuo* (0·5 mm, under N_2) and the residue was taken up in Et_2O (50 ml). The ethereal phase, washed with $NaHCO_3$ aq and dried ($MgSO_4$), was evaporated and the residue rapidly distilled (7 g, 75–80% purity), b.p. 107–110°/2 mm. The crude compound was purified (90–92%) by chromatography over silica gel, eluting with n-hexane–Et_2O (7:3), and subsequent rapid distillation, b.p. 100–2°/1 mm. **9a, b**: IR (film): 2825, 2720, 1720 cm^{-1}. **9c, d**: IR (film): 2830, 2720, 1720 cm^{-1}. (Found: **9a** C, 66·17; H, 10·23; **9b** C, 65·71; H, 10·25; **9c** C, 65·69; H, 9·81; **9d** C, 66·22; H, 9·86. $C_{11}H_{20}O_3$ requires: C, 65·96; H, 10·06%).

3 - *Isopropyl* - 5 - *methoxy* - 6 - *ketoheptanoic acid methylesters* (**10a, b, c, d**). 3% $KMnO_4$ aq (65 ml) was added dropwise to a suspension of purified **9** (3·5 g) in 5% $NaHCO_3$ aq (35 ml), cooled in an ice-bath. The mixture was then centrifuged and the supernatant liquid extracted with Et_2O. The aqueous layer was treated with Na_2SO_3 (1 g) and then acidified with 10% H_2SO_4 and extracted with Et_2O (5 × 30 ml). The ethereal phase was concentrated and then treated with excess CH_2N_2 in Et_2O. The crude (90–93% purity) ester (2·5 g) was purified (98%) by chromatography (silica gel, hexane–Et_2O 7:3) and by distillation, b.p. 124–7°/0·5 mm. **10a, b**: IR (film): 1715 cm^{-1}; **10c, d**: IR (film): 1725 cm^{-1}. (Found: **10a** C, 62·41; H, 9·73; **10b** C, 62·32; H, 9·75; **10c** C, 62·64; H, 9·39; **10d** C, 62·37; H, 9·50. $C_{12}H_{22}O_4$ requires: C, 62·58; H, 9·62%).

2 - *Methoxy* - 4 - *isopropylhexandioic acid dimethylester*. (1) **11c, d**. 5% NaOH aq (40 ml) was added to a rapidly stirred suspension of **10c** or **10d** (2 g) in water (40 ml), cooled by an ice-water bath. An aqueous soln of I_2 and KI (10 and 20% respectively) was then added dropwise, until a definite dark colour remained for 5' (83 ml *ca*). The mixture was extracted with Et_2O, treated with $NaHSO_3$ and acidified (pH 5–6) with 10% H_2SO_4. After extraction with Et_2O and concentration, the residue was treated with excess CH_2N_2 in Et_2O. The dimethylester **11** was isolated by chromatography over silica gel and purified (99%) by distillation (1·2 g), b.p. 169–170°/16 mm; IR (film): 1735 cm. (2) **11a, b**. The reaction, effected according to the above conditions, with 5% NaOH aq being added dropwise so as not to allow the pH to exceed 10, proceeded more slowly and was worked up when the stoichiometric amount of I_2 was added; these dimethylesters are indeed unstable in this media. The pure product (99%) has b.p. 155–7°/13 mm; IR (film): 1730 cm^{-1}. (Found: **11a** C, 58·30; H, 8·87; **11b** C, 58·69; H, 9·12; **11c** C, 58·36; H, 9·09; **11d** C, 58·59; H, 8·79. $C_{12}H_{22}O_5$ requires: C, 58·51; H, 9·00%).

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